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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,572	10/31/2003	Nicholas P. Barker	50206/012002	1119

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EXAMINER	
DUFFY, PATRICIA ANN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,572	BARKER ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *5,8-19 and 23-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 7 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2005X2, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed 3-27-07 has been entered into the record. Claims 1-42 are pending.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-4, 7 and 20-22 of this application. In the instant case, the following is noted with respect to the provisional documents: None of 60/286,240 (drawn to mucositis) 60/327,637 (drawn to dermal); 60/317,657 (drawn to uterine, vaginal and cervical); 60/309,238 (drawn to distal bowel); 60/333,836 (drawn to respiratory); and 60/367,574 (drawn to combination therapy gastrointestinal adverse effects) support the subject matter of claims 1-4, 6, 7 and 22. None of these documents provide written description of claims 20 and 21.

Similarly, the corresponding applications filed under 35 USC 111 for which Applicants claim priority under 35 USC 120, lack written description and enablement for breadth of the now claimed subject matter (10/131,063; 10/266,069; 10/235,238; 10/208,968; 10/305,747; and 10/397,953.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Information Disclosure Statement

The information disclosure statements filed 7-11-05, 7-8-05 and 12-1-04 have been considered. Initialed copies are enclosed.

Election/Restrictions

Applicant's election without traverse of Group I, and speices Intestinal Trefoil Factor and Corneal in the response filed 3-27-07is acknowledged.

Claims 5, 8-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species of Group I, there being no allowable generic or linking claim.

Claims 23-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected invention of Group II, there being no allowable generic or linking claim.

Claims 1-4, 6, 7 and 20-22 are under examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be

commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 7 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-17 of U.S. Patent No.6,221,840.

The species of human ITF administered orally (buccal) to treat the alimentary canal or mouth or esophagus in particular anticipates the instantly claimed invention.

Claims 1, 6, 7 and 20-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No.6,525,018.

The species of ITF, SP and pS2 and biologically active fragments thereof administered to treat a disruption of the corneal epithelium of a patient anticipates the instantly claimed invention.

Claims 1, 6, 7 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 7 of U.S. Patent No.6,063,755.

The species of trefoil peptide administered treat a gastrointestinal disorder includes alimentary canal or mouth or esophagus and thus anticipates the instantly claimed invention.

Claims 1-4, 6-7, and 20-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the specifically indicated claims of copending Application Nos. 10/235,238 (claims 1 and 6-13); 10/266,069 (Claims 1-27); 10/305,747 (claims 1-5 and 7-33), 10/313,642 (claims 1, 3-7 and 10-21), 10/353,334 (claims 7-18), 10/397,953 (claims 12-15, 17, 23-25 and 27-35); 10/431,805 (claims 1-23); 10/434,607 (claims 1-22 and 38-58); 10/434,636 (claims 1-21); 10/434,752 (claims 1-4, 6, 11-21 and 41-51); 10/435,406 (claims 1-21 and 38-51); 10/449,456 (claims 1-6, 9, 10, 13 and 14); and 10/457,157 (claims 1-21), 11/275,599 (claims 2-10). Although the conflicting claims are not identical, they are not patentably distinct from each other because the individual applications recite treatment of epithelial lesions in the mouth or esophagus, skin, eye (i.e the instant corneal), respiratory, genitourinary by administration of various trefoil peptides and fragments thereof and as such anticipate the genus or species (corneal) claims recited herein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

All the claims of this application conflict with numerous claims of multiple different Application Nos 10/235,238; 10/266,069; 10/305,747, 10/313,642, 10/353,334, 10/397,953; 10/431805; 10/434,636; 10/434,752; 10/435,406; 10/449,456; and 10/457,157. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims1-4, 6, 7 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The term "trefoil peptide" is defined in the specification as any polypeptide having at least a trefoil domain and retaining a biological activity characteristic of trefoil peptides. Trefoil domain is defined as a polypeptide having sequence "substantially" identical to any one of SEQ ID NOS:3-6 which correspond to the trefoil domains of hpS2 (30-70), hSP1(30-71), hSP2(80-120) and hITF(24-64) and retain at least on biological activity characteristic of trefoil peptides. The terms "substantially" and "biological activity characteristic of trefoil peptides" are not defined in the specification. The teachings of the specification are limited to specific known trefoil peptides of the art. The specification fails to identify a single fragment, sequence variant of any of the known

trefoil peptide of the art hpS2, hSP1, hSP2 and hITF that retains the biological activity of the native sequences. The specification fails to teach that any of the recited isolated trefoil motifs consisting of trefoil domains recited supra and specifically claimed are able to mediate any biological activity in the absence of the full-length protein. The scope of the term includes numerous variants that merely have undefined structure "substantially identical" and are not required to retain the "trefoil motif" because they can vary from the specifically disclosed trefoil motif in some unrelated structural manner. As such, the term "trefoil peptide" does not constitute a description of the claimed genus. The specification does not place any structure, chemical or functional limitations on the variants of trefoil peptide. The recitation of "a biological activity" would encompass things such as the ability to generate an antibody. The recitation of "trefoil peptide" therefore does not convey a common structure or function in view of the broad all encompassing definitions set forth in the specification. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members are permitted. The specification and the claims do not provide any guidance on the structure of the polypeptide and what changes can or cannot be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the no specific biological activity is required, no structure is required, the definition does not require the trefoil structure, the isolated domains are not disclosed as having any biological activity in the absence of a full length polypeptide, "a biological activity" that encompasses activities such as immunogenicity alone is insufficient to describe the genus of trefoil peptides that function equivalently. One of skill in the art

would reasonable conclude that the disclosure of the known trefoil peptides of the art, fails to provide a representative number of species of peptide to describe the claimed genus. Applicants were not in possession of the claimed genus because the specification does not convey to one of skill in the art a representative number of variants in structure and function of any such polypeptide that has the claimed/structure and function. The genus of polypeptides with the claimed function is substantial and highly variant because the polypeptides do not have a claimed common structure and function. The recitation of "trefoil peptide" does not convey a common structure nor a common function. As such, generic polypeptide sequences that are unrelated via structure and function are highly variant and not conveyed by way of written description by the specification at the time of filing. As such the specification lacks written description for the highly variant genus and one skilled in the art would not recognize that applicants had possession of the genus of claimed polypeptides for use in the assay as instantly claimed.

Claims 1-4, 6-7 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of " preventing or treating epithelial lesions" in of a mammal comprising administering to the lesion or region of the skin where a lesion is to be prevented , a trefoil-domain-containing polypeptide or a trefoil peptide fragment thereof, intestinal trefoil peptide (ITF) or specifically claimed fragments and "substantially identical" variants thereof. This language specifically encompasses treatment and prevention of cancer and benign lesions of the eye, respiratory epithelium, vaginal, uterine, cervical, gastrointestinal and dermal or skin lesions encompassing

bacterial, viral infections such as herpes, warts, discoloration by age spots and the lesions as set forth in claim 21.

The specification fails to teach even one working example that provides for prevention of lesions, treatment of cancer or benign lesions using trefoil polypeptides, in fact the expression of trefoil peptides is correlated with the presence of cancer and invasive cancer (see Rio et al, Science 241:705-708, 1998; of record and Goldenring et al 20020187487 A1). There is no evidence of record that lesions such as cancer or pre-cancerous lesions of any epithelial surface can be treated using any trefoil peptide and the art would suggest that the presence of trefoil factors correlates with the presence of cancerous cells. Therefore, one skilled in the art would have reason to doubt that any trefoil peptide administered in any manner would be able to provide prophylaxis or treat these malignant or benign "lesions" of the epithelium. The specification is devoid of any teaching that the claimed peptides are effective for preventing any damage or disease as it relates to prophylaxis or treatment of the epithelium, encompassed by the definition of treatment in the instant specification. There is no written description of what time to administer the trefoil peptide and to what patient population for prevention or prophylaxis. Without identification of an "at risk" patient population, there is no written description or guidance as to what patients to give the trefoil peptides to prevent lesions. Further, the claims are drawn in part to using particular fragments of ITF (claims 2 and 3) to "treat a lesion". None of the claimed fragments of ITF have been demonstrated to have any biological activity an *in vitro* assay predicative of *in vivo* activity or actual *in vivo* activity for treating or prevention cancer or precancerous epithelial lesions when administered by any means (i.e. oral, topical, inhaled, local or systemic).

There is no written description of what time to administer the trefoil peptide and to what patient population to prevent lesions caused by any means. Without identification of an "at risk" patient population, there is no written description or guidance as to what patients to give the trefoil peptides to prevent lesions. How does the skilled artisan

prevent lesions from a virus, fungal, or bacterial agent or any other means. No trefoil peptide has been demonstrated to have anti-viral, anti-fungal or anti-bacterial activity. The ability of hITF is enhanced migration of corneal epithelial cells is similar to two known growth factors that enhance corneal epithelial wound healing (TGFβ and TGFa) *in vivo*. However, the specification is devoid of any teaching of an effect of any analog or variant encompassed within the broad definition of ITF on prevention or treatment of keratitis (inflammation of the cornea of the eye) of any type or keratoconjunctivitis (the combined inflammation of the conjunctiva and cornea of the eye), no data is presented that indicates that ITF provides for any benefit with respect to "sicca" or dry eye or scarring of the eye tissues (cicatricial penhigoid). The teachings of the specification are not enabling for use ITF in general as broadly defined in the specification, in corneal wound healing because the art teaches that similar structure does not predict similar function. Absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule (i.e. ITF of SEQ ID NO:2 or 4). It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity or structural conformation results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays,

Volume 18, Number 12, pages 973-981{1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)] and Attwood, [Science, 290:471-473, (29 October 2000)]. The specification is devoid of written description of variants, analogs etc as encompassed by the term "ITF" as defined in the specification as filed. The specification fails to teach a single variant of any of the known trefoil peptides (ITF, spasmolytic peptide and pS2). The specification does not teach the critical residues of any trefoil domain containing trefoil peptide for any of the known family of trefoil peptides that are required to perform the function of treating or preventing distal bowel lesions, such that the skilled artisan could even begin to test or screen for sequence homologs, variants or derivatives which would be functional equivalents of the native sequences using conventional technology. The specification fails to teach an *in vitro* assay that is useful for screening variants and is predictive of success *in vivo*. Thus, one of skill in the art would be reduced to merely randomly altering amino acid(s) which would lead to unpredictable results regarding the functional activity of the protein. Protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted *a priori* and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the

mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The specification has not conceived any other functionally equivalent protein sequences of the native sequences or of any fragment thereof. In view of the lack of enabling written description of how to obtain, make and use the trefoil protein variants, one of skill in the art would be unable to produce either the proteins encompassed by the claimed "ITF" terminology. In applications directed to inventions in arts but where the results are unpredictable, and in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). Further, the courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* (CCPA) 153 USPQ 48). In this application, no variants or analogs have been demonstrated to have activity of the parent molecule sufficient to treat lesions as claimed and the art teaches that C-terminal truncations of ITF and mutants unpredictably loose their ability to promote wound healing (Kinoshita et al , Molecular and Cellular Biology, 20(13):4860-4690, July 2000). As to any of the other claimed disorders [including but not limited to keratitis (inflammation of the cornea of the eye) of any type or keratoconjunctivitis (the combined inflammation of the conjunctiva and cornea of the eye) of any type, ophthalmic herpes zoster, ocular inflammation, or scarring of the eye tissues (cicatricial penhigoid)] the specification is not enabled for treatment of any of these eye disorders for the following reasons. Applicant's specification fails to teach any effect of any disclosed trefoil protein on any inflammatory process such as scarring, mitogenesis, production of secondary inflammatory mediators. It is noted that Applicants

own specification and the art teaches that growth factors that have been documented to enhance corneal would healing have disparate effects on inflammation. The specification teaches that TGFβ decrease mitogenesis, TGFa increases mitogenesis, whereas hITF or rITF and SP have no effect on mitogenesis. Thus, the similar functional property of enhancing corneal would healing by promotion of epithelial cell migration does not predict similar effects on mitogenesis or inflammation. The art specifically teaches that epithelial growth factor promotes corneal wound healing but at the cost of an inflammatory reaction (Burling et al, American Journal of Veterinary Research 61(9):1150-1155, 2000). Thus, growth factors that promote wound healing may also promote inflammation. Neither the art, nor the specification as originally filed provides a clear cut correlation of the enhancement activity of corneal wound healing by growth factors with the ability of the same to treat any eye disorder or ocular inflammation. Therefore, in the absence of teachings in the specification that trefoil proteins mitigate ocular inflammation caused by conjunctivitis, herpes zoster or any other mechanism, the treatment of eye disorders or any inflammatory eye disorders of claim 21 is not enabled by this specification at the time of filing.

The term "trefoil peptide" as defined in the specification as any mammalian homologs of human spasmolytic polypeptide, human pS2 and human ITF polypeptides. The homologs of any trefoil peptides have "substantial identity" . The length of comparison sequences of fragments having 20, 30 40 contiguous amino acid residues. The specification does not teach how to identify other trefoil peptide or variants of trefoil peptide that has at least 30% amino acids difference, much less which undisclosed trefoil peptide is effective for treating lesions in the mouth or esophagus or outside the gastrointestinal tract. May et al (Biochemistry 42: 8250-8259, 2003) teach the closely related trefoil peptides such as TFF1 and TFF3 have different structure, distribution of surface charge and divergent biological activities (see abstract, in particular). The specification does not teach which amino acids within the full-length sequence of all trefoil peptide are critical

and can or cannot be change such as substitution, deletion, addition and combination thereof. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. Ngo et al teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Mason et al (Molecular Endocrinology 8(3): 325-332, 1994) teach in activin A, even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason et al further teach an equivalent protein such as TGFI31 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular). In addition to the lack of guidance as to the structure of any and all trefoil peptides, any biologically active fragment thereof, any intestinal trefoil factor (ITF), any spasmolytic polypeptide, any pS2, and any biologically active fragment as claimed, there is a lack of *in vivo* working example showing that any undisclosed trefoil peptide, particularly the fragment thereof of spasmolytic polyeptide, pS2 or ITF in particular is effective for treating lesions in any in vitro model that is correlative with therapeutic efficacy in vivo. The actual biological activity and that of the intestinal trefoil variants, analogs and fragments remain to be demonstrated and described. The specification does not teach any of the trefoil peptides fragments as claimed have any activity in vitro or in vivo. In fact, there is conflicting studies that trefoil peptide such as

ITF2 is expressed in different epithelial tissues (i.e. human respiratory tract). Silva et al (J Pathology 190: 133-142, 2000) teach only trefoil peptide TFF1 and TFF3 are expressed in the upper respiratory tract and restricted to secretory cells, ciliated cells and submucosal cells while trefoil peptide TFF2 are not detectable by immunostaining or Western blot using various antibodies and RT-PCR (see entire document, page 135, col. 2, second full paragraph, in particular). Nikolaidis et al (American J Respiratory Cell and Molecular Biology 29: 458-464, 2003) teach asthma is a complex chronic inflammatory pulmonary disorder and trefoil factor 2 (TFF2) is an allergen induced gene in the asthmatic lung, IL-4 and IL-13 are potent inducer of TFF2. However, trefoil factor 3 (TFF3) are not expressed in the expressed in allergic airway inflammation such as the asthmatic lung (see page 460, col. 1, first full paragraph, in particular). Nikolaidis et al further teach different allergens such as ovalbumin and spergillusfumigatus in two different asthma models (acute inflammation). Specifically, TFF2 induction by both ovalbumin and pharmacologically delivery of IL-4 and IL-13 depend upon signal transducer and activator of transcription STAT6. However, TFF2 induction by both spergillusfumigatus and pharmacologically delivery of IL-4 and IL-13 is independent of signal transducer and activator of transcription STAT6 (see abstract, in particular). The regulatory mechanisms of these processes still remain poorly understood and will require extensive research. As such, treatment of structures outside the gastrointestinal tract using any trefoil peptides or fragments is highly unpredictable, varies depending on the animal model, means of administration and composition of the trefoil peptide. With regard to biologically active fragment as set forth in the claims, there is not a single fragment from the smallest to the largest fragment shows any biological effect for treating lesions outside the gastrointestinal tract, or within the gastrointestinal tract. For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 Fed. Cir.

1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

Their actual activity, and that of ITF *per se* or any part thereof remains to be broadly demonstrated to be motogenic in promoting wound healing at different mucosal surfaces. In addition, the dermis or skin is not a mucosal membrane. The specification and the priority documents fail to teach that any trefoil peptide or domain has activity in any *in vitro* or *in vivo* assay that is predictive of a therapeutic effect for lesions in the treatment in mammals. The specification and that of the priority documents are devoid of any working examples of treatment of lesions of the skin in a mammal. Skin is not a mucosal epithelium. The epithelial structures of the skin are different from that of the mucosal surfaces. Cutaneous (i.e. skin) wound repair is a dynamic interactive process where kerationocytes, fibroblasts and bone marrow-derived cells their cytokines along with other known and unknown factors result in restoration of the injured skin (see column 1, page 125, Introduction, of Juhasz et al, Immunology Letters, 52:125-128, 1996). This process has been found to be highly complicated scenario involving many cytokines and matrix interactions that are not defined in the any epithelium including the gastrointestinal tract where they have been extensively studied (Yoo et al eds: Gastrointestinal Mucosal Repair and Experimental Therapeutics, Front. Gastrointest. Res. Basel, Karger 25:14-28, 2002). Unlike, the gastrointestinal tract, there is no evidence of record that trefoil peptides are present and expressed in wound healing in the skin. There is no evidence that these peptides play any role in wound healing of the skin using *in vitro* or *in vivo* models. There is not evidence in the specification that the skin, dermis or any part thereof have trefoil peptide receptors. Additionally, Modlin et al teach that all trefoil peptides do not have the same biological activities are not expressed in different compartments in the gastrointestinal tract, respond at different rates to injury and do not have identical biological activities (ITF but not SP affects electrogenic chloride transport; page S98, column 1). Tesfaigzi (Archivum Immunologiae et Therapiae

Experimentalis, 51:283-288, 2003) teach that the research to date shows that various steps that occur during the repair process of injured mucosal epithelium. However, regulatory mechanisms of these processes still remain poorly understood and will require extensive research and have not been demonstrated to be readily transposable to other mucosal surfaces, much less surfaces that are populated by cells that are not "mucosal". The research will require expertise from many different backgrounds (page 287, column 1, last full paragraph). Moss et al (Yale Journal of Biology and Medicine 69(2) :155-158, 1997) teach that "...therapeutic agents in current use to heal ulcers were selected empirically, on the basis of symptom relief and healing efficacy *in vivo*. If ultimately we wish to apply the knowledge derived from experimental models and cell culture studies to enhance mucosal repair clinically, we will need to narrow the gap between the more basic sciences and the clinical studies." Additionally, McKenzie et al (Aliment Pharmacol Ther. 14:1033-1040, 2000) teaches that the results on the mode of administration that are promote protection or healing of the gastrointestinal are conflicting. ".. controversy exists surround the property in relation to their dose and route of administration." McKenzie et al teach that the art of Playford et al (1995), showed that subcutaneous but not oral administration of hTFF2 resulted in a reduction of gastric injury. These studies were conflicted by other studies that demonstrated orally but not parenterally administered hTFF2 and hTFF3 cause a reduction in gastric injury. As such, the composition, mode, delivery means and type of trefoil factor composition is not predictive of results in one *in vivo* animal model to another *in vivo* animal model using the best understood repair of gastrointestinal mucosal injury. Therefore one skilled in the art would have substantial reason to doubt that the claimed trefoil peptides would be effective to prevent or treat a lesion of the skin as claimed. The only study on bronchial epithelial cells established that TFF3 (ITF), but not TFF2 provided for migration of bronchial epithelial cells *in vitro* (Oertel et al, American Journal of Respiratory Cell and Molecular Biology, 25(4):418-424, 2001; of record). These and other studies on mucosal

tissue establish that treatment in this area using trefoil peptides is highly unpredictable, varies depending on the animal model, means of administration, and composition of trefoil peptide and it is completely unclear as to how these teachings would translate to wound healing in a non-mucosal tissue. Niether the instant specification, nor any of the priority documents provides for any *in vitro* or *in vivo* examples of effective treatment of the skin. The specification fails to teach efficacy or activity of motility in an *in vitro* model of skin wound healing that is predictive of *in vivo* activity. Even if one were to demonstrate *in vivo* activity, the art studies with gastric healing after injury indicates that the effects of any trefoil peptide are unpredictable when moving from one mode of administration (parental) to another (i.e. oral). Success with one mode does not predict activity with another mode. Further, while a trefoil factor may prevent or reduce gastric mucosal damage by its topical actions, it can fail to stimulate early restitution in the injured gastric mucosa (see abstract, Cook et al, Journal of Gastroenterology and Hepatology 13:363-370, 1998). This art teaches that treatment with trefoil peptides even with the best studied models is contraversial and success with one trefoil peptide does not predict success with the other and that there are substantial questions to be answered with respect to efficacy of route of administration. Further, since the well studied model of the art is a mucosal model, the specification fails to draw a line between the restitution models of the art for gastric mucosal injury and skin injury. In applications directed to inventions in arts but where the results are unpredictable, and in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). Further, the courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* (CCPA) 153 USPQ 48). In this application, none of the fragments,

from the smallest to the biggest has been demonstrated to have activity of the parent molecule sufficient to treat respiratory or airway lesions. Therefore, in the absence of further guidance from Applicants, one skilled in the art could not use these fragments in the absence of testing to see if they would work, without reason to believe any would work, because not a single trefoil peptide has been shown to be effective either *in vitro* or *in vivo*. One skilled in the art would have to test to see if one could use the trefoil peptides and biologically active fragments thereof before performing the claimed method. Further, with respect to the scope of trefoil peptides. This term is broadly defined in the specification as filed. The specification fails to teach a single variant of any of the known trefoil peptides (ITF, spasmolytic peptide and pS2). The specification does not teach the critical residues of any trefoil domain containing trefoil peptide for any of the known family of trefoil peptides that are required to perform the function of treating or preventing skin lesions, such that the skilled artisan could even begin to test or screen for sequence homologs, variants or derivatives which would be functional equivalents of the native sequences using conventional technology. The specification fails to teach an *in vitro* assay that is useful for screening variants and is predictive of success *in vivo*. Thus, one of skill in the art would be reduced to merely randomly altering amino acid(s) which would lead to unpredictable results regarding the functional activity of the protein. Protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted *a priori* and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal

of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The specification has not conceived any other functionally equivalent protein sequences of the native sequences or of any fragment thereof. In view of the lack of enabling written description of how to obtain, make and use the trefoil protein variants, one of skill in the art would be unable to produce either the proteins encompassed by the claimed terminology because no specific assay is provided that is indicative or predictive of in vivo therapeutic efficacy.

The teachings of the specification and art indicate that ITF is effective in enhancing corneal epithelial wound healing by enhancing of the migration of the epithelial cells across the corneal wound. The ability of ITF is enhance migration of corneal epithelial cells is similar to two known growth factors that enhance corneal epithelial wound healing (TGFβ and TGFα) *in vivo*. However, the specification is devoid of any teaching of an effect of the claimed factors on occult infection of the eye, the resulting inflammation, ulceration, or necrosis in any *in vitro* or *in vivo* models that assess such. The exemplified model of restitution does not correlate with treatment of blindness or inflammation for reasons already made of record. Eye disorders resulting from invasion by the claimed microbes has been interpreted as infection. Applicant's specification fails to teach any effect of any disclosed trefoil protein on infection or inflammatory processes caused by infection, production of secondary inflammatory mediators produced during infection or its effect with respect to microbial infection and its correlation with disruption of the epithelium and effective treatment thereof. It is noted that Applicant's own specification and the art teaches that growth factors that have been

documented to enhance corneal would healing have disparate effects on inflammation. The specification teaches that TGFβ decrease mitogenesis, TGFα increases mitogenesis, whereas ITF and SP have no effect on mitogenesis. The art specifically teaches that epithelial growth factor promotes corneal wound healing but at the cost of an inflammatory reaction (Burling et al, American Journal of Veterinary Research 61(9):1150-1155, 2000). Thus, growth factors that promote wound healing may also promote inflammation. Neither the art, nor the specification as originally filed provides a clear cut correlation of the enhancement activity of corneal wound healing by growth factors with the ability of the same to treat eye disorders resulting from disruption of the epithelium and invasion by a microbe. There is no evidence of record that blindness, necrosis or ulcers can be effectively treated using any trefoil factor. Therefore, in the absence of teachings in the specification that trefoil proteins mitigate microbial infections, inflammation caused by conjunctivitis, herpes zoster or any other mechanism, the treatment of eye disorders produced by a wide variety of disparate mechanisms is not enabled by this specification at the time of filing. The specification fails to teach the correlation of eye infection with "disruption of epithelium" and effective treatment of the disruption in any disruption caused by microbial infection. The specification fails to teach that any of the trefoil peptides provides for resolution of corneal wounds or corneal epithelial disruption during any microbial infection caused by bacteria, viruses or fungi. The specification has not shown that the claimed trefoil peptides are effective to treat disruption of a corneal epithelium or any eye epithelium in general in the presence of an ongoing microbial infection (i.e. resulting from invasion by a microbe). Further, treatment of disorders of the eye is defined in the specification is prevention of lesions and there is no evidence of record indicating that any trefoil peptide prevents epithelial disruption caused by microbial infections and the specification is devoid of any assay to test for such. In the absence of further guidance from Applicant, in view of the lack of written description for the claimed methods, the lack of correlation of prevention and treatment

of conjunctivitis, inflammation, blindness, necrosis, ulcers ... caused by ongoing microbial infections and the ability to mitigate or treat such and in view that the art teaches that the ability of a growth factor to enhance wound healing does not correlate with treatment or mitigation of inflammation or viral infections of the eye, it would require undue experimentation on the part of the skilled artisan to so broadly use trefoil proteins for treatment resulting from disruption of the corneal epithelium and invasion by a microbe or affecting the conjunctiva and resulting from invasion by a microbe.

In view of the lack of specific written description variants, the lack of enabling disclosure for prevention or treatment of skin lesions *in vivo*, lack of description that ITF or any of its fragments are functional in skin wound healing, the lack of an enabling written description of how to obtain, make and use the trefoil proteins encompassed by the scope, the unpredictability associated with producing and using the myriad of homologs encompassed in the scope of the claims, the lack of teaching even a beginning point for variation of the protein sequence for routine experimentation, lack of working examples to demonstrate efficacy either *in vitro* or *in vivo* commensurate in scope with the instant claims, the lack of a described assay to screen for such, the skilled artisan would be forced into undue experimentation to practice (i.e. make and use) the invention as is claimed.

Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims, 2-4 the claims recite specific regions of hITF, however, the claims are indefinite in the absence of a corresponding sequence identifier. Further claim 2 is indefinite from the recitation of "EA" because it is unclear what this acronym stands for.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 7 and 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Podolsky, (WO 97/38712, published 23 October 1997; of record).

Podolsky teaches that trefoil factors SP and pS2 and human/rat intestinal trefoil factor (ITF) and its fragments (from about the first cysteine residue involved in a disulphide bond of the three loop structure to about the last cysteine residue involved in disulfide bond of the three loop structure; page 8, lines 1-10) variants thereof and members of the trefoil family, can be used in treatment abrasions of the surface of the eye (i.e. cornea, page 36 second full paragraph), no matter how the injury is caused and treatment of the gastrointestinal tract from damage cause by radiation therapy or chemotherapy by promoting the maintenance of mucosal integrity. Podolsky teaches the treatment of lesions inside and outside the alimentary canal (page 10) including ulcers. As such the claimed invention is anticipated by the reference.

Claims 1, 6, 7 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Podolsky et al (US Patent No. 6,063,755 issued May 16, 2000; of record).

Podolsky et al teach the administration of trefoil factors (SP, pS2, human and rat ITF) used to treat injury of the gastrointestinal tract including radiation injury or other insults (column 3, lines 60-67 and claim 7). As such, the claims are anticipated.

Listing of References

It is noted that the references cited herein have not been provided because they are already of record or have been provided in applications 10/235,238; 10/266,069; 10/305,747, 10/313,642, 10/353,334, 10/397,953; 10/431805; 10/434,636; 10/434,752; 10/435,406; 10/449,456; and 10/457,157.

Status of the Claims

Claims 1-4, 6-7 and 20-22 stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Examiner Jeffrey Siew can be reached on 571-272-0787.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645